

REMARKS

Claims 19-21, 23-24 and 76-90 are pending in this application. Claims 78 and 87 have been withdrawn by the Examiner as being drawn to non-elected inventions.

I. THE CLAIM REJECTION UNDER 35 U.S.C. § 112, FIRST PARAGRAPH, SHOULD BE WITHDRAWN

Claims 19-21, 23-24, 76-77, 79-86 and 88-90 are rejected under 35 U.S.C. § 112, first paragraph, allegedly for lack of enablement. Specifically, the Examiner alleges that Applicants have not taught that plasminogen activator is effective in treating any angiogenic disease, and in particular hemangiomas.

According to applicable case law, “[t]he test of enablement is whether one reasonably skilled in the art could make or use the invention from the disclosures in the patent coupled with information known in the art without undue experimentation.” United States v. Teletronics, Inc., 857 F.2d 778, 785, 8 U.S.P.Q.2d 1217, 1223 (Fed. Cir. 1988). The factors that are relevant in determining what constitutes undue experimentation as set forth in Wands (citing Ex parte Forman, 230 U.S.P.Q. 546, 547 (Bd. Pat. App. & Int. 1986)) include “(1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims.” 858 F.2d 731, 740, 8 U.S.P.Q.2d 1400, 1407 (Fed. Cir. 1988). Any conclusion of non-enablement must be based on the evidence as a whole, and not based on an analysis of only one of the factors while ignoring one or more of the others. In re Wands, 858 F.2d at 740, 8 U.S.P.Q.2d at 1407.

Applicants respectfully point out that the Examiner has not made an enablement rejection over the method *as a whole*. “The invention that one skilled in the art must be enabled to make and use is *that defined by the claim(s)* of the particular application or patent.” See MPEP § 2164 (emphasis added). An enabling description for a process or method requires sufficient disclosure as to “how to carry out *the claimed process*.” In re Barrett, 440 F.2d 1391, 1392 (CCPA 1971) (emphasis added).

The present invention relates to a novel method of treating an angiogenic disease by administering to an animal a therapeutically effective amount of a plasminogen activator that increases the total amount of angiostatin present in said animal (claim 19). When administered, the therapeutically effective amount of plasminogen activator converts endogenous plasminogen to plasmin, which is then converted to angiostatin in the presence of

endogenous sulfhydryl donor(s), resulting in an increase in the amount of angiostatin and a decrease in angiogenic activity in the animal (see specification, page 3, lines 24-28; page 19, lines 4-9). Applicants submit that the amount of plasminogen activator administered in the claimed method is not an amount that does not promote vascularization, nor an amount that would be effective for canceling the effect of vascularization, nor an amount that would produce an adequate amount of angiostatin effective for treating any angiogenic diseases in the presence of the vascularization effect by the plasminogen activator *per se* as required by the Examiner (see Office Action, page 4, line 20 to page 5, line 8), but a *therapeutically effective amount* that *increases the amount of angiostatin* in the animal.

Contrary to the Examiner's allegation, the instant specification fully enables one skilled in the art to make and use the invention commensurate in scope with the claims without undue experimentation as explained below. In particular, Applicants submit that one skilled in the art can make and use the invention, including increasing the amount of angiostatin in an animal to treat an angiogenic disease, such as hemangiomas, by using the teaching from the specification *coupled with* information known in the art.

The Examiner's attention is respectfully directed to page 3, lines 24-28 and page 19, lines 4-9 of the specification. In these sections, the specification discloses methods of treating an angiogenic disease by administering to an animal an amount of a plasminogen activator sufficient to increase the amount of angiostatin in the animal. The amount of plasminogen activator administered is sufficient to cause conversion of plasminogen to plasmin, which is then converted to angiostatin in the presence of endogenous sulfhydryl donors (see specification, page 42, line 24 to page 43, line 4).

The Examiner's attention is also directed to the Declaration of Gerald A. Soff, M.D., Under 37 C.F.R. § 1.132 dated February 13, 2001 ("Declaration"); the Supplemental Declaration of Gerald A. Soff, M.D., Under 37 C.F.R. § 1.132 dated December 4, 2001 ("Supplemental Declaration"); and the Second Supplemental Declaration of Gerald A. Soff, M.D., Under 37 C.F.R. § 1.132 dated October 7, 2002 ("Second Supplemental Declaration") that were submitted in the parent U.S. Application No. 08/991,761, and filed along with the Reply Under 37 C.F.R. § 1.116 filed April 17, 2003 in the present application. Together, the Declaration, the Supplemental Declaration, and the Second Supplemental Declaration show that the administration of a therapeutically effective amount of a plasminogen activator alone increases the amount of angiostatin in an animal (see Declaration, paragraphs 9 and 14; Supplemental Declaration, paragraphs 17-21 and Exhibit 5; Second Supplemental

Declaration, paragraph 3) and induces anti-angiogenic activity in the animal (see Declaration, paragraphs 17-19 and Exhibits D and E).

The Examiner's attention is now invited to the Declaration of Gerald A. Soff, M.D., Under 37 C.F.R. § 1.132 ("§ 1.132 Declaration") submitted concurrently herewith. The experiments described therein have been performed. The data reported in the § 1.132 Declaration concerns the successful treatment of an angiogenic disease in mice by administering to said mice angiostatin which was generated in the presence of a plasminogen activator and endogenous sulfhydryl donor. First, the results demonstrate that a plasminogen activator alone is effective to generate angiostatin in human plasma by first converting plasminogen to plasmin, which is then converted to angiostatin in the presence of a sulfhydryl donor that is either endogenously present or from an exogenous source (see § 1.132 Declaration, paragraph 12). The sulfhydryl donor from an endogenous source is present in an amount that is sufficient to convert the increased amount of intermediate plasmin to angiostatin and, therefore, increases the total amount of angiostatin present in the animal (see § 1.132 Declaration, paragraphs 11 and 14). Third, the results demonstrate that mice with s.c. hemangioendothelioma treated with affinity-purified human angiostatin generated by the administration of a plasminogen activator alone had significantly reduced tumor volume, increased survival, and avoided the onset of splenomegaly and hematological complications, as compared to control mice (see § 1.132 Declaration, paragraphs 12-16). Together, the results as shown in the § 1.132 Declaration demonstrate that when administered alone, in the presence of endogenous sulfhydryl donor, the dose and dosage regimen of plasminogen activator can be adjusted to generate levels of angiostatin that have a clinical benefit in patients with an angiogenic disease such as hemangiomas.

Applicants submit that no undue experimentation is required for one skilled in the art to which it pertains, to make and use the present invention commensurate in scope with the claims. The amount of direction or guidance presented is plenty. As discussed in detail above, the specification and declarations referenced herein clearly teach and fully describe the present invention, *i.e.*, the administration of a therapeutically effective amount of a plasminogen activator to increase the amount of angiostatin that induces anti-angiogenic activity in the animal (see specification, page 3, lines 24-28 and page 19, lines 4-9; Declaration; Supplemental Declaration; and Second Supplemental Declaration) and, therefore, resulting in the treatment of an angiogenic disease in the animal (see § 1.132 Declaration).

Moreover, Applicants submit that the quantity of experimentation necessary to make and use the present invention is not great. The present invention requires the administration of a therapeutically effective amount of a plasminogen activator to increase the total amount of angiostatin in an animal in order to treat an angiogenic disease. Here, the specification not only provides exemplification on how to determine if angiostatin is generated (see page 32, lines 9-15) and how much angiostatin is generated (see page 36, lines 7-11), the specification also provides exemplification on how to determine the amount of angiostatin required to inhibit angiogenesis (see page 34, line 5 to page 35, line 22). Applicants submit that only routine experimentation is required to determine the amount of angiostatin generated due to the administration of a plasminogen activator. Applicants also submit that only routine experimentation is required to determine the amount of angiostatin useful for treating an angiogenic disease of interest. It would be well within the abilities of the skilled artisan to apply and monitor the biochemical assays that measure the amount of angiostatin generated and the level of anti-angiogenic activity. As such, Applicants submit that based on the teachings of the specification and information known in the art, one skilled in the art would know how to determine what a therapeutically effective amount of plasminogen activator is in order to produce an amount of angiostatin useful for treating an angiogenic disease.

The Examiner did not arrive at a conclusion of non-enablement based on the evidence as a whole. Rather, the Examiner applied only one *Wand* factor under the test for undue experimentation. Specifically, the Examiner alleges that testing angiogenic diseases, including hemangiomas, using a plasminogen activator is unpredictable in view of the teaching of Berman et al. (Invest Ophthalmol Vis Sci. 1982;22(2):191-9). The Examiner arrived at a conclusion of non-enablement based on an analysis of only one of the factors while ignoring one or more of the others. This is improper. *In re Wands*, 858 F.2d at 740, 8 USPQ2d at 1407. Applicant submits that when all of the *Wands* factors are considered, one of ordinary skill in the art can determine without undue experimentation the therapeutically effective amount of a plasminogen activator that would be sufficient to produce the claimed effect, *i.e.*, increase angiostatin and reduce angiogenic activity in an animal. Accordingly, the instant specification fully enables one of skill in the art to make and use the invention commensurate in scope with the claims without undue experimentation.


In view of the foregoing, the rejection under 35 U.S.C. § 112, first paragraph, should be withdrawn.

CONCLUSION

Entry and consideration of the foregoing remarks and the § 1.132 Declaration into the file of the present application is respectfully requested. Withdrawal of all rejections and an allowance of the application are earnestly requested. If any issues remain in connection herewith, the Examiner is respectfully invited to telephone the undersigned to discuss the same.

Respectfully submitted,

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